Ergogenic Aids: A Review of Basic Science, Performance, Side Effects, and Status in Sports

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The use of drugs and supplements to enhance performance has become a part of mainstream athletics. Many team physicians and sports medicine practitioners are unfamiliar with the benefits and risks of these products and thus are unable to educate young athletes on this topic. In spite of numerous reports on the health risks of anabolic steroid use, 1 to 3 million Americans have used them. Human growth hormone has been tried by up to 5% of 10th graders, although no scientific study has shown that it is an effective performance-enhancing drug. Amphetamines and similar compounds may be the most widely abused drug in baseball; recently, they have come under increased scrutiny in sport. Erythropoietin is a highly effective aerobic enhancer that has been linked to multiple deaths in cyclists and other endurance athletes. The neutraceutical industry, led by supplements such as creatine, ephedra, and androstenedione, remains unregulated by the Food and Drug Administration and has serious issues with quality and side effects. An understanding of these products is essential for the sports medicine practitioner to provide sound, safe advice to the athlete.

Keywords: performance-enhancing drugs; anabolic agents; steroids; stimulants

In 1995, a poll of 198 Olympic-level power athletes offered the following scenario: you are offered a banned substance with 2 guarantees. First, you will not be caught, and, second, by taking the substance you will win. Of the athletes asked if they would take the substance, only 3 said they would not. The poll went on to propose that the same undetectable substance would enable you to win every competition entered for the next 5 years but then would kill you. More than half of those polled reported that they would still use the substance.[6]

The poll results[6] lend insight into why performance-enhancing substances remain a core discussion in competitive sports. As athletics becomes more competitive and lucrative, many athletes turn to chemical performance enhancement. In an anonymous survey of 26 USA Powerlifting Team members who competed internationally since 1988, 15 returned questionnaires. The survey solicited yes-no responses about current and previous use of anabolic steroids in power lifting. Analysis indicated that 10 of the 15 team members admitted to use of these drugs, and 5 of those admitted to beating the International Olympic Committee's (IOC's) doping control procedures.[25]

More recent reports reveal that this phenomenon is not limited to the Olympic athlete. In a survey of high school football players in Indiana, Stilger and Yesalis[92] noted a use rate of more than 6%, with a mean age for initiation of use at 14 years. Fifteen percent of users in that study[92] began use before the age of 10. In addition, a survey of more than 1600 Canadian students, sixth grade and above, self-reported a usage rate of 2.8%. Of those who admitted using steroids, 29% reported injecting them, and 29% of those reported sharing needles for injection.[64] Fifty-four percent of all users thought steroids were bad for them.[64]

Although anabolic steroids have received the most attention as ergogenic aids, a number of other substances have come under scrutiny in more recent years. Human growth hormone (hGH) is rumored as a widely used anabolic agent, in spite of no scientific evidence that it improves strength, power, or athletic performance. Amphetamines are rumored to be the most commonly abused drug in professional baseball. Professional cyclers and others in endurance sports use erythropoietin (EPO). The supplement industry, led by makers of creatine and

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androstenedione (andro), has become a multimillion-dollar-per-year industry.

Regulation of these various ergogenic aids is an extremely difficult task. Testing for banned substances requires expensive and ever-improving techniques to keep up with so-called designer drugs that have been chemically altered to avoid detection. In addition, several ergogenic aids are so similar to naturally occurring body substances that testing is all but impossible. Even with detection, governing bodies are often not equipped with the resources to defend test results against the inevitable legal battles that come with suspension of an athlete.

The purpose of this article is to review the impact, basic science, performance benefits, and potential health risks of the most commonly used performance-enhancing substances, as well as the policies for dealing with these substances.

ANABOLIC STEROIDS

In spite of numerous reports of health risks associated with their use, anabolic steroids remain a widely abused drug. It is estimated that 1 to 3 million athletes in the United States alone have used anabolic steroids,[88] with annual black market sales well in excess of $100 million.[101] Among American adolescents, use rates generally range between 4% and 12% among young men and are as high as 2% among young women.[2] Adolescent steroid users are far more likely to engage in other high-risk behaviors, including multiple drug use, smoking, suicidal behavior, sexual activity, weapon possession, and needle sharing,[65] than are their classmates. Although these findings are alarming, intervention programs targeted to educate adolescents about proper strength and nutrition can be successful in changing attitudes and decreasing use.[63,69]

Recently, there has been increasing concern over so-called designer steroids. These are simple chemical modifications of known banned anabolic steroids that will not be detected in existing testing protocols. The most popular of these is tetrahydrogestrinone (THG), and it is currently under intense scrutiny after being detected in several athletes. The drug, which has been linked to the Bay Area Laboratory Co-operative, was originally detected at a University of California Los Angeles laboratory after a coach sent an anonymous tip and a sample to the laboratory. Since then, several professional and Olympic-caliber athletes have tested positive for the steroid, and the investigation is currently ongoing. Although there are no published data on THG and its role in human performance, one could reasonably conclude that its chemical similarity to other anabolic steroids would make it likely to have similar results and side effects to others in that class.

Basic Science

Anabolic-androgenic steroids (AAS) are chemically modified analogs of testosterone, the endogenous hormone primarily responsible for male sexual characteristics and muscle anabolism. First isolated in 1935,[86] AAS have been modified many times to maximize the anabolic effects of the drug and to minimize the androgenic effects by alkylation of the 17-alpha position or carboxylation of the 17-beta hydroxyl group on the sterol D ring. These analogs are degraded much more slowly than endogenous testosterone is, resulting in a higher prolonged concentration of the analog.

The physiologic action of AAS is thought to be similar to native testosterone. The molecule diffuses across the cell membrane after binding to a receptor. This complex then binds to the nucleus of a cell, stimulating messenger RNA synthesis, which leads to an increase in structural and contractile protein.[18] In addition, AAS are thought to combat the catabolic effects of cortisol through competitive inhibition of the glucocorticoid receptor and are thought to have a direct neural action through androgen receptors on alpha motor neurons.[101]

Performance Studies

Results of clinical trials evaluating anabolic steroids are difficult to evaluate because of methodological and dosing differences. Some studies have shown minimal effects on body composition and strength,[24,35] whereas others have shown that supraphysiologic doses of testosterone or its derivatives can lead to an increase in fat-free mass and muscle size and strength in humans.[10,34,40] In studies using higher dosing over longer periods, the effects seem to be more pronounced. In a prospective, placebo-controlled study of testosterone enanthate (TE) with and without exercise over a 10-week period, Bhasin et al[10] showed that supraphysiologic weekly doses of TE increased triceps (505 mm^2 difference) and leg area (738 mm^2 difference) as well as strength in the bench press (10 kg difference) and squat (17 kg difference) in subjects not engaged in strength training. In addition, those subjects assigned to TE administration and exercise had greater increases in fat-free mass (6 kg) and muscle size as well as strength (22 kg increase in bench press, 38 kg increase in squat) than did those assigned to either no-exercise group. The authors concluded that supraphysiologic doses of TE, especially when combined with strength training, lead to an increase in fat-free mass, muscle size, and strength in normal men.

In another study of the effects of anabolic steroids on body composition and strength,[40] 21 weight-training men were randomly assigned in a double-blind fashion to either TE or placebo for 12 weeks, with a 12-week follow-up period. The TE group had significant increases in body weight, fat-free mass, arm girth, rectus femoris circumference, and libido compared with that of the placebo group. The TE group also experienced an increase in systolic blood pressure, frontal alopecia, mild acne, and subjective changes to personality including increased aggression and irritability. The authors concluded that moderate doses of TE combined with weight training can result in short-term changes in upper body strength and composition, with changes to baseline health in some individuals.

Forbes et al[34] also studied the effects of testosterone on healthy subjects, and in addition, they studied the effects on these subjects after the drug was stopped. These

authors found that TE administration led to a progressive increase in lean body mass and a decrease in body fat. They also found that body composition reverted slowly toward normal when the injections were stopped but that the effects of the drug lingered for some time. They concluded that testosterone is a powerful anabolic agent that can have profound and lasting effects on body composition.

These types of results have led to the use of anabolic steroids (1) in the treatment of conditions such as HIV,[83] (2) for the constitutional delay of growth,[73] and (3) in the normal aging process.[91]

Side Effects

Studying the side effects and health risks of anabolic steroid use in athletes is difficult. Because the drugs are illegal, there is a paucity of well-controlled studies available for review. Inconsistencies in type, dosing, and training habits often make it difficult to draw statistically valid conclusions. Thus, we find conflicting results in the literature. Nevertheless, a number of studies[‖] have investigated the health consequences associated with these drugs and have provided strong evidence of their risks, including hepatic cellular damage, testicular atrophy, cardiovascular disease, and psychological disturbance.

With regard to cardiovascular effects, there appears to be an association between an atherogenic blood lipid profile and endothelial dysfunction with steroid use. Ebenbichler et al[28] studied blood lipid profiles and flow-mediated dilatation (FMD) as an indicator for endothelial function in 20 nonsmoking male bodybuilders and compared their results with those of nonsmoking controls. The authors found that during a steroid cycle, bodybuilders decreased high-density lipoprotein (HDL) and FMD and that they suppressed luteinizing hormone and follicle-stimulating hormone levels compared with controls. In addition, FMD was decreased both during and after completion of a steroid cycle. The authors concluded that intake of anabolic steroids is associated with both an atherogenic blood lipid profile and endothelial dysfunction and, thus, may pose an increased risk of atherosclerosis.[28]

In another study, Kuipers et al[57] found that anabolic steroids induced a 25% to 27% decrease in HDL cholesterol and an increase in diastolic blood pressure after 8 weeks of use. The authors found no significant changes in liver enzyme levels, and the blood pressures and HDL abnormalities had returned to normal by 6 weeks after cessation of drug use. In a follow-up study by the same group,[49] steroid users were examined for a number of cardiovascular risk factors after 3 months of cessation of use of the drug. The authors found no differences in blood pressure, lipoprotein profiles, or liver enzyme levels compared with those of controls. These findings suggest that the negative cardiovascular effects induced by anabolic steroids may be reversible. It should be noted that the dosing recorded in these studies may be far less than those used out of a controlled environment. Other studies[33,94] have cited anabolic steroid use associated with hypertension, myocardial ischemia, and sudden cardiac death.

Another area of concern with anabolic steroids is the potential psychological effects associated with their use. Cooper et al[23] found that anabolic steroid use directly caused significant disturbances in personality profile as assessed by the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed, rev). In addition, a study by Midgley et al[66] showed anabolic steroid users reported being significantly less in control of their aggression than did controls.

Other authors have taken a more bottom-line approach to the study of side effects associated with anabolic steroid use. Parssinen et al[74] compared mortality rates among elite power lifters suspected of steroid abuse with those of population controls. The authors found that the mortality rate during the 12-year follow-up was 12.9% in the bodybuilders compared with 3.1% in the control population. The causes of death among the power lifters included suicide, acute myocardial infarction, hepatic coma, and non-Hodgkin's lymphoma. Although the power lifters were "strongly suspected" of steroid use, no actual documentation of rate, dosing, or chronicity was established in the study. In another study on cause of death among steroid abusers, Thiblin et al[96] investigated the demise of 34 known users of these drugs. Nine users were victims of homicide, 11 had committed suicide, 12 deaths were judged accidental, and 2 causes of death were not determined. Chronic cardiac changes were observed in 12 cases. The authors concluded that anabolic steroid use was associated with an increased risk of violent death from impulsive, aggressive behavior or depressive symptoms.

An additional and perhaps underappreciated health risk associated with the use of anabolic steroids is that of infection associated with needle sharing. Rich et al[79] reported a 25% rate of needle sharing among adolescent anabolic steroid users. Human immunodeficiency virus, hepatitis B and C, and abscesses have been documented among anabolic steroid injectors who share needles.[80]

Testing and Policy

Overall, AAS are generally available only with a physician's prescription. This class of drugs is banned and tested for by the IOC and most American sporting organizations, including the National Collegiate Athletic Association (NCAA), the National Football League (NFL), and the National Basketball Association. Major League Baseball does not test for these agents, although recent claims by former players have led to congressional hearings on the topic. Testing for anabolic steroids is fraught with complications, as there is considerable variation among normal results, testing is expensive, a positive result often results in costly legal ramifications, and newer versions of drugs that go undetected are being developed rapidly. One example of how far the legal battles have pushed the testing issues is shown in what is considered a negative test result for testosterone. According to the Olympic Movement Anti-doping Code, a test for illegal testosterone supplementation is considered to have a positive result if

[‖]References 23, 28, 33, 49, 57, 66, 74, 79, 80, 94, 96.

the ratio of testosterone to epitestosterone is 6 or greater. A normal man's ratio rarely goes above 1.3. In fact, only 1 in 1000 men has a ratio of 4. The allowable ratio is 6:1; this is also the standard for women.

HUMAN GROWTH HORMONE

Human growth hormone is an endogenous peptide secreted by the anterior pituitary gland. It is known to have metabolic functions that are generally anabolic, increasing amino acid uptake and protein synthesis as well as supporting other growth-promoting bodily functions. Patients who are deficient in hGH are short in stature. Conversely, patients with conditions that are characterized by an overabundance of hGH have the clinical condition known as gigantism and are hallmarked by the large size that justifies its name. Because of this, athletes have attempted to stimulate growth by supplementing with this hormone. Because the drug is illegal except under the prescription of a physician, well-controlled studies are lacking and its impact is largely unknown, although the rumors of its use abound throughout the sports world. In a study of 432 10th graders in the Midwest, Rickert et al[81] reported that 5% of those queried responded that they had taken hGH. Those users had a high association with anabolic steroid use and reported a first use at a mean age of 14 to 15 years. Most hGH users were unaware of any potential side effects of the drug.

Basic Science

Much of the basic science of hGH remains unknown. The hormone is a 191-residue, 22kDa peptide that is released from the anterior pituitary gland. Secretion of hGH is regulated by a number of factors, including growth hormone–releasing hormone, sleep, exercise, L-dopa, and arginine.[101] The half-life of hGH is short but does stimulate the release of somatomedins like the insulin-like growth factors. In addition, hGH stimulates renal and hepatic gluconeogenesis as well as lipolysis.[101]

Animal studies have shown that administration of recombinant hGH leads to muscle hypertrophy, but this is not accompanied by increases in strength.[62] In acromegaly, increased hGH levels lead to larger but functionally weaker muscles.[62]

Performance Studies

Little research has been done with hGH supplementation. That which has been done is generally in populations with endocrine dysfunction. One study in critically ill patients showed that patients treated with hGH experienced higher rates of morbidity and mortality than did their nontreated counterparts.[19] Another study of hGH supplementation in elderly men with low endogenous hGH levels showed that hGH had no effect on muscle strength at any time in the study.[95] Yarasheski,[102] in his review, reported that daily growth hormone treatment modestly increases nitrogen retention in most normal adults but only for a few weeks. Resistance seems to occur with longer use. The author stated that it is doubtful that nitrogen retention results in an increase of contractile protein and improved muscle function, strength, or athletic performance. Supplementation with hGH did lead to increases in lean body mass, but with further investigation, these increases were noted to be nonmuscular. In a further review by Frisch,[36] the author reported that although hGH may lead to an increase in size of a muscle, it is not associated with an increase in strength or performance. He also stated that in weight lifters, the incorporation of amino acids into skeletal muscle protein was not increased with hGH supplementation. These authors[36,95,102] concluded that there is no evidence that growth hormone supplementation will lead to an increase in performance.

Side Effects

From the experience with acromegalics, it is known that high levels of hGH over long periods of time can lead to muscles that are myopathic.[62] Side effects also include water retention, carpal tunnel syndrome, and insulin resistance.[102]

Testing and Policy

Only through a physician's prescription is hGH available. It is banned by the IOC, although Olympic participants are not officially tested for hGH. Testing in professional sports in the Unites States awaits an accurate method.

AMPHETAMINES AND OTHER STIMULANTS

The use of stimulants as ergogenic aids has had a long history in sport. With the recent deaths of an NFL lineman and a Major League Baseball pitcher who were reportedly supplementing with ephedrine, this class of drugs has come under scrutiny and has been banned by the NFL. In Major League Baseball, the drugs commonly referred to as "beans" or "greenies" have been in some locker rooms since the 1960s. In an informal poll of one major league club conducted during spring training, several players estimated that more than half of the players on their current or past teams regularly used amphetamines. Although certainly not scientific, this information suggests that stimulants remain the most commonly abused drug in baseball. In addition, ephedrine has become a popular player in the supplement industry, with claims that it boosts metabolism, burns fat, and increases alertness. These claims have made it popular among pilots, truck drivers, and the general population. Supplements such as the Chinese herb *ma huang* or *guarana* have similar actions to amphetamines.

Basic Science

Amphetamines are chemically related to the catecholamines, with the exception of the hydroxyl groups at the meta and para positions of the benzene ring that they share in common. They have an indirect action on cate-

cholamine metabolism. In this way, they stimulate the release of norepinephrine from sympathetic nerves, resulting in vasoconstriction and increased blood pressure. In addition, mood elevation and resistance to fatigue have also been reported through a dopaminergic pathway.[22] Ephedrine has a similar mechanism of action.

Performance Studies

Although not normally studied for their ergogenic potential, several studies have evaluated the effect of amphetamine on performance. One such study noted improvements in quadriceps strength and anaerobic capacity with Dexedrine administration. The study showed no increase in VO_2 max, but it did show increases in time to exhaustion, suggesting resistance to fatigue.[21] Other authors[39] have noted that pseudoephedrine given before testing induced significant improvements in maximum torque, peak power during cycling, and lung function. Still other studies[7,8] have shown that the drugs were effective in decreasing medium-distance run times.

Side Effects

The use of amphetamines has been associated with a number of negative side effects, including anxiety, ventricular dysrhythmias, hypertension, and hallucinations. In addition, use among weight lifters has been associated with dependence and addiction.[45]

Testing and Policy

Several amphetamines and stimulants are available over the counter. Most classes are banned by the IOC, and several forms are prohibited in American professional sports. As mentioned above, the NFL has recently banned ephedrine.

ERYTHROPOIETIN AND BLOOD DOPING

Because endurance athletes are particularly sensitive to the oxygen-carrying capacity in their blood, any substance that increases this capacity provides a tremendous aerobic advantage. This advantage is evidenced by the long-recognized practices of living at altitude and sleeping in altitude tents. Another method of accomplishing this increase is through blood doping, which involves an autologous transfusion of previously donated blood after a period of hematocrit recovery or through a homologous transfusion from a cross-matched donor. These transfusions artificially increase the hematocrit mass and thus the oxygen-carrying capacity of blood. An alternative to doping, the drug EPO increases hematocrit when administered in a recombinant form.[59] This drug is effective and does not require the initial donation of blood or potential risks of transfusion to achieve the increase in hematocrit. It is perceived to be effective enough that many cyclists and other aerobic athletes consider EPO to be an occupational necessity at the sports' highest levels. Rumors of its widespread use abound. At least one athlete was removed from the 1996 Olympic games in Atlanta for use of this drug.[101] Evidence of the impact of hemoglobin enhancement was studied by Videman et al,[98] who looked at changes in hemoglobin values in elite cross-country skiers over a 12-year period. Mean values at the beginning of the study were lower than population reference values, as would be expected from volume expansion achieved during endurance training. However, an increase was noted beginning in 1994 and continued to peak at dangerous values. After institution of a rule that limited hemoglobin values in these athletes, a sharp decline in maximum hemoglobin was noted. The authors concluded that the rule had achieved its goal of limiting extreme hemoglobin values but that the mean hemoglobin values in cross-country skiers continued to rise, suggesting continued use of "artificial methods" to raise hemoglobin mass.

Basic Science

Erythropoietin is a hormone naturally produced in the kidney. Once released, it serves to stimulate an increase in hemoglobin. In this way, it increases the oxygen-carrying capacity of the blood. Williams and Branch[101] reported that an increase of 1 g/dL of hemoglobin in an athlete with an exercise cardiac output of 25 L/min would increase oxygen transport by 335 mL, which extrapolates to an 8% increase given a normal VO_2 max of 4000 mL O_2/min. Lavoie et al[59] investigated the effects of recombinant EPO (rEPO) on metabolism in rats. The authors found that 15 days of rEPO administration resulted in a significant increase in hematocrit. In addition, they found that exercised rats in the rEPO group had higher muscle glycogen and free fatty acids and lower lactate levels compared with those of controls. The results suggest that energy substrate use during exercise is affected by enhanced oxygen availability. They concluded that supplementation with rEPO resulted in a lower contribution of anaerobic metabolism to energy production.[59]

Performance Studies

Although popular since the 1960s, blood doping was not extensively studied until later decades. Williams and Branch[101] summarized studies on the various effects of blood doping with ample volumes and time for recovery in trained athletes. With blood doping, approximate findings included a 7% increase in hemoglobin, a 5% increase in VO_2 max, a 34% increase in time to exhaustion at 95% VO_2 max, and a 44-second improvement in 5-mile treadmill run time performance.

Although few studies on the ergogenic potential of rEPO have been done, a few recent studies[12,30] have come to similar conclusions to those achieved in studies of blood doping. Birkeland et al[12] performed a double-blind, placebo-controlled study of 4 weeks of rEPO supplementation using a cycle ergometer to measure effects. The authors reported that in rEPO subjects, hematocrit increased from 42.7% to 50.8%. In addition, VO_2 max increased from 63.6 to 68.1 mL · kg–1 · min–1, a 7% increase. Neither outcome

measure showed a significant increase in the placebo group. Similar findings were noted by Ekblom and Berglund.[30] They reported a 6% to 11% increase in hematocrit and increases in VO_2 max in time to exhaustion after 7 weeks of rEPO administration.

Side Effects

Artificially raising hemoglobin levels can have dangerous consequences. In 1987, the first year of EPO release in Europe, 5 Dutch cyclists died of unexplained reasons. Between 1997 and 2000, 18 cyclists died from stroke, myocardial infarction, or pulmonary embolism. These events have brought the drug into the forefront of discussion in endurance sport. Ramifications like these prompted the American College of Sports Medicine to take a position stand against the use of any ergogenic aid designed to artificially raise hemoglobin mass, calling them unethical and unfair, and they stated that this practice exposes the athlete to unwarranted and potentially serious health risks.[84]

Blood transfusions, when conducted under standard hospital procedures, are a safe and effective method to increase red blood cell mass. Even in these conditions, however, risks of infection with such pathogens as HIV and hepatitis, as well as transfusion reactions, require a detailed informed consent discussion. The unsupervised practice of transfusing blood products would assuredly increase those risks. In addition, raising one's hematocrit beyond physiologically normal levels leads to an increase in blood viscosity, thrombogenic potential, and myocardial infarction risk. These outcomes have been reported in cyclists who have supplemented with rEPO.[76]

Testing and Policy

The drug EPO is available only by a physician's prescription. It is not legal in any sport. Since the 1996 Atlanta Olympics, gas chromatography–mass spectrometry evaluations have been used for screening of exogenous EPO in the urine. Recently, high-performance liquid chromatography has also been used to detect subtle peptides in the urine.[13] Despite these recent advances, exogenous EPO remains a particularly difficult substance to detect through tests. Organizations that ban its use, such as the IOC, the United States Olympic Committee, and the International Cycling Union, face a considerable challenge in detecting and eliminating this drug from competitive athletics. One governing body has used an upper limit of hemoglobin as a rule for competition. This rule resulted in dramatic decreases in the hemoglobin values in world-class skiers.[98]

CREATINE

Since its introduction in 1992, creatine has become the most popular nutritional supplement on the market.[55] According to the *Nutrition Business Journal*, sales in the year 2000 were estimated at more than $300 million in the United States alone, a 3-fold increase since 1997. Like many supplements in the so-called neutraceutical industry, there is no required federal assessment of quality, performance, or safety with creatine, and thus the marketing of the supplement is far more advanced than its science.

Although discovered by Chevreul in 1832, according to Todhunter,[97] the first reported use of creatine by elite athletes occurred during the 1992 Barcelona Olympics.[29] The evidence was reported in British track and field athletes. Creatine use has become popular in anaerobic sporting events. Several prevalence studies of its use among college athletes quote a usage rate of 41% to 48% among men.[43,58] In a recent survey of NFL trainers and team physicians, all teams had players actively taking the supplement, with estimates of use averaging 33% and reports as high as 90% (Tokish, unpublished data, 2002).

Basic Science

Creatine is a naturally occurring compound made from the amino acids glycine, arginine, and methionine. Primarily synthesized in the liver, pancreas, and kidney, 95% of the creatine is stored in skeletal muscle. These stores are broken down at a relatively constant rate of 2 g/dL into creatinine, which is excreted by the kidney. Exogenous sources of creatine include fresh fish and meat—but in small amounts that do not equal the estimated 2 g daily turnover.[5] Creatine concentrations in skeletal muscle average around 125 mmol/kg of dry muscle,[42] with a higher capacity for storage in type II muscle fibers.[20] In its phosphorylated form, creatine contributes to the rapid resynthesis of adenosine triphosphate during short-duration maximal bouts of anaerobic exercise. This mechanism forms the basis for creatine supplementation.

In 1992, Harris et al[47] showed that oral creatine supplementation resulted in a significant increase in the total creatine content of the quadriceps femoris muscle, in some subjects reaching as high as 50%. Further studies by Balsom et al[4] have shown that creatine supplementation may put off or decrease anaerobic glycolysis during brief maximal exercise. These mechanisms may enhance anaerobic training, leading to strength and performance gains in these athletes.

Performance Studies

Human performance with creatine supplementation has been studied extensively. Typical designs of these studies have been longitudinal, prospective, randomized, and placebo controlled. Each study population was a relatively small group of athletes. Athletes were evaluated with a sport-specific test before and then after a period of creatine supplementation, usually for a duration of several weeks.

In weight lifters, the number of repetitions at a specified percentage of single-repetition maximum goes up approximately 20% to 30% after a short-term creatine supplementation period.[27,56,93]

In cyclists, most studies have shown that creatine supplementation is effective in maintaining muscular force and power output.[4,11,26,82] In swimming, performance has

been measured with repeated short sprints of maximal intensity. Results have been mixed, with some studies showing a significant reduction in sprint times,[44,61] whereas others have found the opposite and concluded that creatine supplementation is not effective in swimmers.[17,67] Differences in these studies may be attributed to different outcome measures, the complex mechanics of the swimming stroke, or different supplementation regimens.

In track and field sprinters, several studies have shown an improvement in mean sprint times in the range of 1% to 2%,[1,48,68,85] whereas authors[50,78] of 2 other studies concluded that creatine had no effect on single sprint times.

In terms of body composition changes, creatine supplementation appears to increase weight and lean body mass[4,5,42,56] by around 1 to 2 kg over a short-term supplementation cycle.

There have also been studies in which creatine has been shown to be ineffective. These areas include supplementation in the older athlete (60-87 years of age)[90] and most aerobic endeavors,[31,32] although the latter study did find an approximate 18% benefit in the final "kick" phase of an aerobic event.

A summary statement on these studies would be that creatine can be an effective ergogenic supplement maximized when used for simple, short-duration, maximal-effort anaerobic events.

Side Effects

Since the introduction of creatine in the early 1990s, there have been a number of isolated case reports of possible renal side effects associated with its use.[41,54,75] Although creatine is commonly thought to lead to dehydration, to date, there has been no study that has demonstrated a negative side effect with the use of creatine in athletes. It should be cautioned, however, that the studies that have been done are mostly short term and pertained to healthy individuals. We do not know the long-term effects of this supplement, nor do we have sufficient data on its possible effects on other creatine-containing tissues such as the brain, cardiac muscle, or testes.[51] In addition, several authors[9,46,84,87] caution that long-term administration of creatine will likely lead to the down-regulation of the creatine transporter protein and, thus, an increased resistance to the compound. This effect has been authenticated in a rat model.[46]

Thus, it appears that short-term supplementation with creatine is safe, although much more research needs to be done to investigate long-term effects, possible harm to other tissues, and the consequences of down-regulation.

One additional drawback to creatine deserves further mention. Because it is not classified as a drug, creatine is not under direct regulation by the Food and Drug Administration. This is a problem receiving much attention throughout the supplement industry, and although there is effort to control nutritional supplements in the United States, the quality of individual brands of creatine and other nutritional supplementation remains far from uniform. This lack of uniformity makes creatine difficult to study and harder to control.

Testing and Policy

Creatine is available over the counter in several nutritional supplements. It is not tested for or banned by any major athletic organization. The NCAA does have a policy that none of its member teams will provide creatine to their players. In a recent survey of NFL trainers and team physicians, 40% of NFL teams provided creatine for their players, although in no case was the medical staff involved in this distribution (Tokish, unpublished data, 2002).

BETA-HYDROXY-BETA-METHYLBUTYRATE

Beta-hydroxy-beta-methylbutyrate (HMB) is a leucine metabolite that has recently gained popularity as an "anti-catabolic." This supplement is marketed to suppress protein breakdown in the recovery phase after a workout, thereby burning only carbohydrates and fat for energy and increasing lean body mass. Studies have examined this supplement's effects on lean body mass, strength, postexercise eccentric muscle damage, and side effects.

Basic Science

The mechanism by which HMB may function is not known. Some have postulated that it may act through increasing the testosterone-epitestosterone ratio, similar to anabolic steroids. Slater et al,[89] however, showed that supplementation with HMB over 2 weeks resulted in no significant increase in the urinary testosterone-epitestosterone ratio, and they concluded that this supplement does not work through a testosterone-mediated pathway.

Other researchers have postulated that HMB supplementation may delay the onset of markers of anaerobic metabolism. Vukovich and Dreifort[99] examined VO_2 peak and lactate accumulation in cyclists in a prospective, randomized double-blind trial of HMB versus placebo over three 2-week supplementations. The authors noted that although VO_2 peak was unaffected by HMB supplementation, the onset of blood lactate accumulation, a marker of anaerobic metabolism, was significantly increased in the HMB group compared with controls.

If HMB is to work as a protein breakdown suppressor, then it would follow that supplementation with HMB should decrease the concentration of markers of muscle damage. This hypothesis has been tested by Knitter et al,[53] who examined the effect of HMB supplementation on creatine phosphokinase and lactate dehydrogenase activities before and after a long run in a prospective, randomized, placebo-controlled 6-week trial. The authors found that the HMB group exhibited significantly lower creatine phosphokinase and lactate dehydrogenase levels than did controls and concluded that HMB supplementation may prevent exercise-induced muscle damage. Several other authors[70-72] have noted similar findings.

Performance Studies

A number of studies have evaluated the effects of HMB supplementation on various markers of human performance. It has been shown that although upper body strength[72] and peak torque generation[37] may show modest improvements after HMB supplementation in untrained individuals, measures such as bench press and leg press one-repetition maximum in trained individuals are not affected by HMB.[37,56,89] When performance with this supplement is examined based on body composition changes, the results are modest at best. Some studies[37,70-72] have shown significant increases in fat-free mass and decreases in body fat percentage of around 1% over that of controls, whereas other studies[56,89] have shown no significant changes in body composition after HMB supplementation.

Thus, although there is some evidence that HMB may act to suppress protein breakdown, there is little evidence in the literature to support that this translates into an ergogenic advantage.

Side Effects

There have been only a few studies on the side effects of HMB supplementation. Gallagher et al[38] evaluated these effects on hematologic, hepatic, and renal function. Although an increase in basophils was noted in the HMB group, no effect was noted on glucose, blood urea nitrogen, hemoglobin, hepatic enzymes, lipid profile, or total leukocytes. In addition, no change in urinalysis was noted. The authors concluded that HMB supplementation is safe for these systems in healthy individuals over an 8-week period. In a comprehensive review, Nissen et al[71] evaluated 9 previous studies done on the safety of HMB supplementation. They found that HMB had no negative effects on blood chemistry. In addition, in review of all the studies, HMB supplementation lowered total cholesterol, low-density lipoprotein cholesterol, and systolic blood pressure. These findings suggest that HMB supplementation appears to be a safe practice and may be cardioprotective.

Testing and Policy

Finally, HMB is available in many over-the-counter nutritional supplements. It has not been banned by any sporting organization to date.

ANDROSTENEDIONE

Androstenedione has gained immense popularity as an over-the-counter ergogenic aid since Mark McGuire admitted to using it during his historic 1998 chase of Roger Maris's single-season home run record. Available since the 1930s, andro is marketed as a supplement that can raise testosterone levels in the blood, thus functioning as a natural alternative to anabolic steroids. It is the immediate precursor to testosterone, and andro is thought to work by being degraded into free testosterone. As with many of the so-called neutraceuticals, the marketing of this supplement's effectiveness far exceeds its science.

Basic Science

The concept of how andro works is based on the knowledge of the effectiveness of testosterone as an ergogenic aid. It is a natural precursor to testosterone. It has been postulated that if the concentration of andro is increased, it will allow for conversion to testosterone and, thus, a more anabolic profile. This claim has been evaluated by a number of studies.[3,14-16,52,77,100] Whether testosterone is increased with andro supplementation is still being debated. The majority of well-designed studies[3,14,52,77,100] showed no increase in testosterone concentrations with supplementation. Investigators of 2 studies[15,60] have found an increase in testosterone with supplementation. What has been shown in the science but that is absent from the marketing is that all major studies on andro supplementation have shown a significant increase in estrogen concentration, a most unergogenic effect.

Performance Studies

Androstenedione supplementation has been studied for ergogenic properties such as lean body mass changes and strength increases.[14,52,100] No study has shown a significant ergogenic effect of any kind with andro supplementation.

Side Effects

A number of studies have evaluated the effects of andro supplementation on blood lipid profiles.[14,16,52] In each of these studies, supplementation has been shown to lower HDL profiles and, thus, may pose a cardiovascular risk. In addition to this, Broeder et al[14] have shown that supplementation with andro may lead to the down-regulation of endogenous testosterone synthesis.

Testing and Policy

Androstenedione is available in many over-the-counter nutritional supplements. It is banned by the IOC, NCAA, and NFL, but it is not banned by Major League Baseball.

SUMMARY

A critical review of the literature reveals that substances that improve performance, or are even perceived to improve performance, are widely used by athletes. The risks and benefits of these products are often poorly understood by the athlete as well as coaches and staff (Table 1). The "just say no" approach to advising the athlete about these supplements will continue to fail because there is such a potent marketing influence to take these supplements and such a powerful drive in athletes to find a competitive advantage. An understanding of the science, or

TABLE 1
Quick Reference Guide of Ergogenic Aids[a]

Ergogenic Aid	Street Name	Desired Effect	Adverse Side Effect	Banned by
Human growth hormone	hGH	May stimulate body growth to increase muscle mass	May develop resistance to long-term use; myopathic muscles; carpal tunnel syndrome	IOC
Erythropoietin	EPO or doping	Increases endurance; increases the oxygen-carrying capacity of the blood	Increases blood viscosity; myocardial infarction; pulmonary embolism	All sports
Anabolic steroids	Testosterone or "T"; designer steroids	Increase muscle mass; decrease body fat	Hepatic cellular damage; testicular atrophy; cardiovascular disease; atherosclerosis; hypertension; myocardial ischemia; sudden cardiac death	IOC, NCAA, NFL, NBA, MLB
Creatine		May enhance anaerobic training; increased strength and performance	May lead to dehydration; long-term side effects at any dose are unknown	None
Beta-hydroxy-beta-methylbutyrate	HMB	May suppress protein breakdown	Unknown	None
Amphetamines	Beans or greenies	May lead to increased reaction time and endurance	Anxiety; ventricular dysrhythmias; hypertension; hallucinations; addiction; death	IOC
Ephedrine	*Ma huang*; *guarana*	Boosts metabolism; burns fat; increases alertness; increases endurance	Anxiety; ventricular dysrhythmias; hypertension; hallucinations; addiction	IOC, NCAA, NFL, recently in United States
Androstenedione	Andro	May lead to increased testosterone production	Unknown; may pose a cardiovascular risk	IOC, NCAA, NFL

[a]IOC, International Olympic Committee; NCAA, National Collegiate Athletic Association; NFL, National Football League; NBA, National Basketball Association; MLB, Major League Baseball.

lack thereof, behind ergogenic aids is essential for those who care for athletes. Team physicians, trainers, and coaches must give meaningful and safe advice to these athletes.

CONCLUSION

With the increased emphasis on athletic performance, it is unlikely that ergogenic aids will go away. It is therefore incumbent on those who look after athletic teams to become educated about these products and to stay current with new supplements as they emerge. It is important that athletes understand that these products are not regulated by the Food and Drug Administration, and thus their contents may not match their labels. In addition, there is very little effort on the part of the manufacturers to investigate side effects or potential downsides to these supplements. Therefore, anyone who takes these products must proceed with extreme caution.

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